Journal of Surgical Oncology 62:30–33 (1996)

Germ Cell Testis Cancer: 15-Year Review

PATRICK KELTY, MD, HAROLD FRAZIER, MD, KEVIN O'CONNELL, MD, AND BIMAL C. GHOSH, MD
From the Departments of Urology (P.K., H.F., K.O.'C.), and Surgery (B.C.G.), National Naval Medical Center, Bethesda, Maryland

Testis cancer affects 2–3 men per every 100,000 in the United States, making it the most common solid tumor of men in the 20–35-year-old age range. Since the average age of active duty military personnel is included in the age range of those at greatest risk for germ cell testis cancer, it is of pertinent clinical importance to physicians who treat these young patients. The National Naval Medical Center has been using cisplatin-based protocols since the time of their introduction. This study reviews the success of treating these patients and examines the treatment failures. © 1996 Wiley-Liss, Inc.*

KEY WORDS: **testis cancer, cisplatin, germ cell tumors, retroperitoneal lymphadenectomy**

INTRODUCTION

Testis cancer affects 2–3 men per every 100,000 in the United States, making it the most common solid tumor of men in the 20–35-year-old age range [1]. Prior to the introduction of platinum-based chemotherapy, patients with nonseminomatous germ cell tumors (NSGCT) had a dismal prognosis [2]. However, since the mid-1970s when cisplatin-based chemotherapeutic protocols were introduced, survival has increased to almost 95%, independent of stage at diagnosis [2].

Since the average age of active duty military personnel is included in the age range of those at greatest risk for germ cell testis cancer, it is of pertinent clinical importance to physicians who treat these young patients. The National Naval Medical Center has been using cisplatin-based protocols since the time of their introduction. This study reviews the success of treating these patients and examines the treatment failures.

MATERIALS AND METHODS

A retrospective review was conducted on patients who underwent treatment for germ cell testis cancer at NNMC from 1978–1992. All cases of germ cell tumors were included, and patients had to be followed for a minimum of 2 years.

Following radical orchiectomy, the specimens underwent pathologic examination to confirm the diagnosis of germ cell tumor. Staging in all patients was determined by physical exam, plain radiography of the chest, tumor markers (alfa-fetoprotein and beta human chorionic gonadotropin), liver function tests, computed tomography (CT) of the abdomen and of the chest, lymphangiography (in the late 1970s and early 1980s), and retroperitoneal lymphadenectomy (RPLND) for patients with NSGCT when indicated.

Patients diagnosed with pathological stage I NSGCT were followed after the RPLND. Patients with stage II and III NSGCT were treated with either three or four cycles of cisplatin, vinblastine, and bleomycin (PVB) or cisplatin, VP-16, and bleomycin (PEB). After chemotherapy, some of these patients underwent an RPLND to resect residual tumor mass found on follow-up studies.

Patients diagnosed with stage I and low volume stage II seminoma were treated with external beam radiation of 2,500–3,000 rad over a 3-week period. Bulky stage II and stage III seminoma patients were treated with PVB or PEB chemotherapeutic protocols.

Follow-up, which included physical exam, tumor markers, and plain chest radiography, was obtained monthly for the first year, every other month for the second year, and semiannually to annually thereafter. A

Accepted for publication December 18, 1995.

Address reprint requests to Dr. Harold Frazier, Department of Urology, PO Box 217, National Naval Medical Center, Bethesda, MD 20889-5000.

The opinions herein represent the authors' opinions and do not necessarily reflect those of the Department of the Navy or the Department of Defense.

TABLE I. Testicular Germ Cell Tumor Types From the National Naval Medical Center, 1978–1992

Cell type	Incidence rate
Seminoma	43.2%
NSGCT	56.8%
Mixed cell type	38.6%
Teratoma	4.6%
Embryonal carcinoma	12.6%
Choriocarcinoma	0.4%

TABLE II. Testicular Germ Cell Tumor 2-Year Survival Rates as Related to Stage, 1978–1992

Stage	Survival (%)
I	127/128 (99.6)
II	59/60 (98.3)
III	21/27 (77.8)

TABLE III. Two-Year Survival Rates as Related to Testicular Germ Cell Type Independent of Stage, 1978–1992

Cell type	Survival
Seminoma	98.9%
Embryonal carcinoma	89.5%
Mixed cell type	92.8%
Teratoma	88.0%

follow-up CT of the abdomen was obtained at 3, 6, 12, and 24 months. Outcome was assessed by cancer-specific survival.

The variables evaluated in the analysis included age, race, tumor cell type, stage at diagnosis, type of chemotherapeutic protocol used when applicable, organ systems involved at the time of diagnosis, and lymphovascular invasion in the original testis tumor. Tumor recurrence and survival of pairs of subgroups were tested for statistical significance by Chi-square.

RESULTS

A total of 215 cases of testis cancer were reviewed during the time frame of the study. Median follow-up was 4 years with a range of 2–11 years. Table I demonstrates the incidence of cell types.

The survival rate of these patients independent of stage was 96.3% (207/215). The stage-specific 2-year survival rates are shown in Table II. Most notably, the survival rates for stages I and II were 99.6% and 98.3% respectively, whereas stage III patients have a 77.8% survival rate. Table III demonstrates the cell type 2-year specific survival independent of stage at the time of diagnosis.

The overall recurrence rate was 7.4% (16/215), and the median time to recurrence was 8 months with a range of 1–24 months. One seminoma recurred to the retroperitoneum 2 years after radiation therapy. This recurrence was successfully treated with the PVB protocol. There were 15 cases with NSGCT that recurred in this cohort. The majority (14/15) recurred in the lung, and one of these 15 recurrences was in the retroperitoneum. In this one case of recurrence in the retroperitoneum, the patient had a clinical stage I teratoma with yolk sac elements, did not undergo an RPLND, and was consequently placed in an observation protocol. There was also a case of lymphoma 6 years after PVB treatment for a NSGCT. This patient has been successfully treated for his lymphoma.

There were only eight deaths during the study's time period. In review of these deaths, one patient died from progressive pulmonary fibrosis secondary to bleomycin toxicity. Four of the patients who died form cancer initially presented with tumor involvement in three or more organ systems at the time of diagnosis. Statistical analysis of these deaths with Chi-square demonstrates that the involvement of three or more organ systems at the time of diagnosis is a poor prognostic feature in patients with NSGCT ($P < 0.001$).

Another poor prognostic indicator was the presence of lymphovascular or rete testis invasion in the primary tumor. All patients who had recurrence of their tumor had lymphovascular or rete testis invasion (16/16) as compared to only 26.6% (53/199) of the survivors who had no recurrence ($P < 0.001$). Comparison of PVB and PEB protocols with respect to recurrence and survival over the 15 years of the study demonstrated no statistical difference.

Examination of the racial composition of this cohort shows that 5/215 (2.3%) were African-Americans. Each of these patients had a chief complaint of either an enlarging testis mass and/or testicular pain. The average age in this subgroup was 22.6 years as compared to 27.4 years in the white patient subgroup. The types of tumors present were equally divided with two seminomas and three mixed germ cell tumors. Although this is a small subgroup and few conclusions can be made, these data do show that African-Americans present with the same symptoms but at an average lower age than those in the Caucasian subgroup. As in the Caucasian subgroup, African-Americans responded well to treatment since there were no deaths or recurrences in this cohort.

There were 12 patients (5.6%) who had a prior history of an undescended testicle. All of these patients had an orchidopexy prior to the tumor being discovered. Examination of the cell types in the tumors within this subgroup demonstrated that 50% were seminomas and 50% were NSGCT (mixed cell type). In 10 of these patients, the tumor was detected on the ipsilateral side as the undescended testis. In two patients, the tumor occurred on the contralateral side. The average age at time of diagnosis was 23.5 years.

Two patients were found to have bilateral tumors within the time frame of the review. In each instance, the patient's original tumor was seminoma, and he recurred to the contralateral testicle with seminoma. In each instance, the patients were treated successfully with chemotherapy.

DISCUSSION

Although germ cell tumors account for only 1–2% of cancer cases, they do represent tumors that are highly curable in a young patient population. Prior to the age of cisplatin, NSGCT had a poor prognosis. The 2-year mortality for stage I patients was 26%, and for stages II and III the mortality was 93% [3]. However, now that cisplatin-based chemotherapeutic protocols are utilized, survival has markedly improved.

Many authors have demonstrated the various prognostic features of NSGCT. Several authors have shown that the presence of embryonal cell elements and lymphovascular invasion in the original testis tumor portend a higher pathologic stage and a higher risk of relapse [4–6]. In addition, the involvement of three or more organ systems at the time of diagnosis may predict a poorer prognosis [5]. The explanation of this is that lymphovascular and rete testis invasion in the original tumor demonstrates the aggressiveness of the tumor and the proclivity of the tumor to metastasize to the retroperitoneum and other organ systems such as lung, mediastinum, and liver [5,6]. Although this study recapitulates the results seen in previous studies, it is one of the larger reviews of testis cancer from a single institution and draws from a large spectrum of patients.

The PVB and PEB protocols now being used at NNMC have been very successful. However, since survival rates are high and these patients are living longer, more long-term complications from the chemotherapy are being seen. In one of the eight deaths from testis cancer at this institution, the patient died from pulmonary fibrosis, a well-known side effect of bleomycin. Unfortunately, attempts to remove bleomycin from various chemotherapeutic protocols have caused reduced survival [7]. In order to combat against pulmonary complications and the possible induction of other cancers, the number of cycles currently used to treat these patients has been reduced in recent years to a minimum [7].

Both PVB and PEB have been implicated in the induction of secondary cancers. Thus far, only one of the 215 patients has developed a secondary malignancy. He presented 6 years posttreatment with lymphoma and has been successfully treated for this malignancy. Other instances of secondary cancers have been reported in the literature, the most common being lymphoma [7]. The overall long-term effects of cisplatin-based chemotherapeutic protocols are not known and are currently being examined.

This study also shows the low incidence of testis cancer in African-Americans. Although the study population is small, the incidence correlates with previous studies [8]. In a multicenter review of testis cancer in African-Americans, Moul et al. [8] demonstrated an incidence of 2.9% with a similar histologic distribution. The overall age of African-Americans tends to be lower at presentation than in the Caucasian subgroup, but due to the small size of this cohort, no definitive conclusions can be made. As to prognosis, there is no difference between these two subgroups. Both have an excellent prognosis. Moul et al. made similar observations [8]. No satisfactory explanation has been proposed to explain the lower incidence of germ cell tumors in African-Americans. One theory proffered is that the increased testosterone levels in African-American women during pregnancy may provide a protective effect to the developing germinal epithelium [9]. This theory is still under investigation.

The history of cryptorchidism is a well-known risk factor for testis cancer. The incidence of 5.6% in this present study is slightly lower than a previous series, which demonstrated a 9.8% incidence [10]. The relative risk of patients developing a germ cell tumor in an undescended testicle is between 5–40-fold when compared to those without cryptorchidism [11]. Theoretically, this increased risk occurs because the seminiferous tubules are exposed to an increased temperature and the tubules do not mature properly. This may cause a malignant transformation [10]. This theory is supported by the observation that an abdominal testicle has a higher risk of malignant changes when compared to inguinal testicles [10].

Another theory is that the testicle has developed abnormally from the start. It is this abnormal development that has caused the testicle not to descend properly into the scrotum, predisposing the organ to malignant transformation [10,12]. This theory would also support the previous observation that an abdominal testis would have an even higher risk of malignant changes. Various studies examining chromosomal analysis of undescended testes have either supported or refuted this theory [13,14].

Each of the patients in this series had undergone a prior orchidopexy to correct their cryptorchidism. There was no differentiation as to the level of the testis at the time of orchidopexy or of the age of the patient when the orchidopexy was done. Although most authors would agree that early orchidopexy probably does not decrease the incidence of germ cell tumors, it does allow the patient and the physician to follow serial examinations and discover a palpable tumor sooner.

The recurrence and survival rates in this study are comparable to previous large scale multicenter studies [4,5,15]. This once again demonstrates the superiority of using a cisplatin-based chemotherapy over previous protocols and the very high survival rates that can be obtained.

CONCLUSIONS

Over the last 15 years, the treatment for testis cancer has undergone a vast improvement. Survival of these

young patients, independent of stage, is now in the 93–96% range due to the introduction of cisplatin-based chemotherapeutic protocols. This 15-year retrospective study from a single institution drawing on a national pool of patients demonstrates this enhanced survival (96%) and reduced recurrence with the use of these agents. Although these protocols have induced high survival rates, the various morbidities from their use are now being seen, and modifications to the treatment regimens are being investigated to minimize the complications. Patients with certain features indicative of a poorer prognosis can now be identified. These patients can be treated aggressively and monitored more closely in the hopes of an earlier discovery and treatment if recurrence does occur.

REFERENCES

1. Richie JP: Neoplasms of the testis. In Walsh, PC, et al. (eds): "Campbell's Urology." Philadelphia: W.B. Saunders, 1992, p 1222–1263.
2. Einhorn L, Donohue J: Cis-diamminedichloroplatinum, vinblastine, and bleomycin in disseminated testicular cancer of the testis. Ann Intern Med 87:293–298, 1977.
3. Sesterhann IA, Weiss RB, Mostofi FK, et al.: Prognosis and other clinical correlates of pathologic review in stage I nonseminomatous testicular carcinoma: A prospective clinicopathologic study. J Clin Oncol 10:69–76, 1992.
4. Alderice JM, Merret JD: Factors influencing survival of patients with testicular teratoma. J Clin Path 38:791–792, 1985.
5. Javadpour N, Young JD: Prognostic factors in nonseminomatous testicular cancer. J Urol 135:497–503, 1986.
6. Javadpour N, Canning DA, Henrickson H, et al.: Predictors of recurrent clinical stage I nonseminomatous germ cell tumors of the testis: Multivariate analysis of a prospective multicenter study. Urology 27:508–512, 1986.
7. Giwercman A, Grindsted J, Hansen B, et al.: Testicular cancer risk in boys with maldescended testis: A cohort study. J Urol 138:1214–1216, 1987.
8. Roth B, Nichols CR: Chemotherapy for testicular cancer: 1994. AUA Updates XII:174–179, 1994.
9. Moul JW, Schanne FJ, Thompson IM, et al.: Testicular cancer in blacks: A multicenter experience. Cancer 73:388–393, 1994.
10. Henderson BE, Berstein L, Ross RK, et al.: The early in-utero oestrogen and testosterone environment of blacks and whites: Potential effects on male offspring. Br J Cancer 57:216–218, 1988.
11. Martin DC: Malignancy in the cryptorchid testis. Urol Clin N Am 9:371–376, 1982.
12. Mostofi FK, Price EB: Tumors of the male genital system. In "Atlas of Tumor Pathology," 2nd Series, Fascicle 8. Washington, D.C.: Armed Forces Institute of Pathology, 1973, p 7–20.
13. Mininberg DT, Bingol N: Chromosomal abnormalities in undescended testicles. Urology 1:98–102, 1973.
14. Dewald GW, Kelalis PP, Gordor H: Chromosomal studies in cryptorchidism. J Urol 117:110–113, 1977.
15. Donohue JP, Zachary JM, Maynard BR: Distribution of nodal metastases in nonseminomatous testis cancer. J Urol 128:315–320, 1982.